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Costs of Hematopoietic Cell Transplantation: Comparison of Umbilical Cord Blood and Matched Related Donor Transplantation and the Impact of Posttransplant Complications

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Allogeneic hematopoietic cell transplantation (HCT) is a complex and costly procedure. Unrelated umbilical cord blood (UCB) is an alternative graft source for patients without matched related donors (MRD); however, costs of UCB HCT have not been described. We compared the costs of HCT within the first 100 days among recipients of MRD (myeloablative = 67, nonmyeloablative = 54) or UCB (myeloablative = 63, nonmyeloablative = 110) HCT. Cost and hospitalization data were obtained from the institutional accounting department. The 100-day probabilities of overall survival (OS) and cumulative incidence of treatment-related mortality (TRM) were comparable among 4 transplant types; however, neutrophil recovery was delayed and graft failure was more likely in UCB recipients. The median cost per day survived (excluding costs of graft acquisition) was $1016 for myeloablative MRD, $2082 for myeloablative UCB, $612 for nonmyeloablative MRD, and $1156 for nonmyeloablative UCB recipients, respectively ($P < .001$). In multivariate analysis, adjusting for important patient, disease, and HCT-related characteristics, as well as major post-HCT complications, factors associated with higher costs within the first 100 days were myeloablative UCB HCT (relative risk 1.3 [95% confidence intervals, 1.1-1.5] versus myeloablative MRD HCT), graft failure (1.8 [1.7-1.9]), need for dialysis (1.3 [1.1-1.5]) or mechanical ventilation (1.3 [1.2-1.4]) and total hospital stay in the highest tertile (>48 days; 2.1 [1.9-2.3]). The median cost per day survived for patients with graft failure was $6976 (versus $1105 for no graft failure), dialysis was $4764 (versus $1102 for no dialysis), and $5099 for mechanical ventilation (versus $977 for no mechanical ventilation). Within the first 100 days, the absolute costs of myeloablative and nonmyeloablative UCB are higher than myeloablative and nonmyeloablative MRD transplantation. These costs are primarily driven by severe posttransplant complications, graft failure, and prolonged inpatient stay. Strategies to enhance engraftment will decrease the costs of UCB transplantation.

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INTRODUCTION

Although hematopoietic cell transplantation (HCT) has the potential to cure high-risk hematologic and nonhematologic disorders, it is a complex, resource-intense, and costly procedure. Costs of transplantation can include charges for delivery of care (eg, physician charges), supportive care (eg, blood product transfusions), graft procurement, hospitalization, pharmacy, and laboratory and radiologic investigations. Also, despite major advances in transplant techniques and supportive care practices, HCT continues to be associated with substantial treatment-related mortality (TRM) such as infections, organ failure, and graft-versus-host disease (GVHD), and management of these complications can further increase the overall cost of posttransplant care. Studies of transplantation costs are complex and difficult to conduct because of the wide variation in transplant methods, conditioning, and GVHD prophylaxis regimens and supportive care practices. However, studies have described costs of allogeneic HCT using either myeloablative or nonmyeloablative conditioning regimens, and show that HCT in general is an

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expensive procedure, and occurrence of complications after transplantation increases overall medical costs [1-10].

Introduction of unrelated umbilical cord blood (UCB) as an alternative graft source for patients without a matched related donor (MRD) is among the most significant recent breakthroughs in the field of transplantation. UCB has the advantages of rapid availability, and may be associated with lower risks of GVHD, despite the use of units with higher HLA disparity [11,12]. Our group has described the use of UCB HCT in adults, especially using 2 UCB units to optimize cell dose with outcomes comparable to that seen with other donor sources [13-15]. However, use of UCB is associated with delayed engraftment and a higher risk of graft failure. Incremental experience is rapidly leading to adoption of UCB as an alternative donor source by many transplant centers. A better understanding of the costs of UCB HCT is of importance from the health care resource utilization and health policy perspective, and can also assist in comparison of cost-effectiveness of UCB with other alternative (eg, matched unrelated donor and haploidentical) donor sources. Identification of specific factors that may be predictive for UCB transplant costs can help with the development of strategies to reduce costs while maintaining outcomes with a resultant increase in the applicability of UCB HCT.

We conducted a retrospective cohort study in a contemporary group of adult HCT recipients to evaluate the costs of myeloablative and nonmyeloablative UCB HCT, and to compare them with the costs of myeloablative and nonmyeloablative MRD HCT. We also explored various risk factors for their association with increased costs of HCT.

PATIENTS AND METHODS

Patients

The study cohort consisted of consecutive patients who received an allogeneic HCT between 2004 and 2006, and were ≥18 years of age at the time of transplantation. From the 318 eligible patients, 24 were excluded: recipients of planned autologous HCT followed by nonmyeloablative allogeneic sibling donor HCT for multiple myeloma (MM; N = 12), and recipients of matched unrelated donor grafts (N = 12). Hence, the final study cohort consisted of 294 patients. Transplant-related and outcome data were retrieved from the University of Minnesota Blood and Marrow Transplant Program Database, which prospectively collects these data on all patients transplanted at our institution. Additional data for this study were abstracted from patient medical records. Patients were treated on clinical protocols approved by our institutional review board.

Conditioning regimen intensity (myeloablative [MA] versus nonmyeloablative [NMA]) was prospectively determined by transplant protocols. Specific indications for HCT using NMA conditioning were older age (≥55 years for MRD and ≥45 years for UCB), presence of significant comorbidity (serious organ dysfunction, invasive mold infection within 3 months before transplantation or Karnofsky performance score of 50-60), or previous extensive prior therapy (>12 months of alkylator-based chemotherapy, >6 months of alkylator-based chemotherapy and extensive radiation, or history of autologous transplantation). Patients received UCB as a graft source if they had no HLA-compatible related donors. Our UCB selection criteria for adults have been previously published and allow the use of 2 UCB units to optimize cell dose, if necessary [12].

Patients were classified as having standard or high risk disease. Standard risk disease included acute leukemia in first complete remission (CR1), chronic myelogenous leukemia (CML) in first chronic phase, myelodysplastic syndrome (MDS) (refractory anemia only), and nonmalignant hematologic disorders; all other diagnoses were categorized as high-risk disease.

Conditioning Regimen and Supportive Care

MA and NMA regimens used at our institution have been described previously [13,14,16]. Briefly, patients undergoing MA MRD HCT received a regimen consisting of total-body irradiation (TBI) and cyclophosphamide (Cy), whereas recipients of MA UCB HCT received TBI, Cy, and fludarabine (Flu). NMA regimens for both MRD and UCB recipients consisted of TBI, Cy, and Flu. The TBI dose in MA regimens was 1320 cGy (165 cGy twice daily ×4 days) and in NMA regimens was 200 cGy (single fraction). Our GVHD prophylaxis and treatment regimens have also been described previously [17]. All patients received GVHD prophylaxis with cyclosporine (CsA; days −3 to at least +100), with trough levels maintained between 200 and 400 ng/mL and either methotrexate (MTX; in MA MRD recipients) or mycophenolate mofetil (MMF; in MA and NMA UCB and NMA MRD recipients; days −3 to at least +30).

Outpatient clinical evaluation to determine eligibility for transplantation was performed within 30 days prior to transplantation for all patients, and included history and physical examination, bone marrow biopsy and aspirate evaluation, assessment of organ function, determination of infectious markers, and appropriate radiologic imaging or other investigations for disease staging. Allogeneic HCT recipients were then admitted to the inpatient unit for initiating conditioning therapy and were discharged from the hospital after they had engrafted (absolute neutrophil count

[ANC] $> 0.5 \times 10^9$/L for 3 days), had adequate oral intake, had transfusion or other infusion requirements that could be met as an outpatient, and had no complications requiring continued hospitalization. Frequency of outpatient follow-up was based on patient overall clinical condition and need for ongoing support (eg, transfusions, antibiotic infusions). All apheresis procedures for MRD peripheral blood stem cell (PBSC) collection were performed as an outpatient. All patients received antibacterial, antiviral, and antifungal prophylaxis and blood product and nutritional support per institutional guidelines. Granulocyte-colony stimulating factor (G-CSF) was administered to all patients until the ANC was $>2.5 \times 10^9$/L for 2 days.

All patients are followed within our transplant program and institution from the time of pretransplant evaluation until at least 100 days posttransplant. Patients are required to stay within a 30-min driving distance from our transplant center, and accommodation is arranged for patients who do not live locally. All hospitalizations within the first 100 days are exclusively in a dedicated inpatient transplant unit that has resources for management of severe post-HCT complications (eg, mechanical ventilation, dialysis, pressor support). All outpatient visits within the first 100 days occur in our transplant clinic, which has infusion chairs and resources for performing minor procedures. Hence, our institutional accounting department captures all relevant medical costs for the first 100 days except costs for outpatient prescription drugs, including drugs administered through home-care services. Transplant-related care in this early posttransplant period was coordinated by our group of transplant physicians and midlevel providers who periodically rotate through both the inpatient and outpatient services and take care of all HCT recipients irrespective of their underlying diagnosis or transplant type. Therefore, individual provider practice variation did not have a major influence on costs within specific transplant types in our analysis.

Cost Data

Data regarding inpatient costs, days of hospitalization, and number of outpatient clinic visits were obtained from the institutional accounting department for all transplant-related costs prior to day 0 (from day −30) and until day 100 posttransplantation. Costs were determined by each hospital department's item and procedure specific costs and then summed from the itemized listing of each patient's hospital accounting record through day 100. Besides total cost of care (direct and indirect costs), specific categories of costs were also available. These categories included costs for "graft acquisition," "laboratory services," "radiologic investigations," "pharmacy services," "room and board," "blood components," and "other services." Examples of "other service" costs include costs for occupational therapy, physical therapy, and vascular access and operating room costs. We excluded costs for "physician services." Also, we could not account for outpatient prescription drug costs and did not include patient related nonmedical costs (eg, out-of-pocket costs, transportation, and accommodation) in our analysis.

Costs for "graft acquisition" consisted of costs for donor evaluation, apheresis procedure, and graft processing and storage for MRD HCT. For UCB recipients, this category included costs for searching the cord blood bank inventory, confirmatory HLA-typing of the cord blood unit, and shipping of the product. Median graft acquisition costs were $9566 for MRD and $68,830 for UCB transplantation. Although patients receiving matched unrelated donor HCT were excluded from this study, their median graft acquisition costs were $55,121. We excluded costs for graft acquisition from further cost analyses, as we wanted to specifically focus on the impact of posttransplant events on total costs. However, graft acquisition costs for a second graft infusion for graft failure or donor lymphocyte infusion for relapse within the first 100 days were included in cost analyses and were combined with the "other" category.

Because our data consisted of the actual dollar amount for cost incurred and given the relatively contemporary nature of our cohort, we did not adjust for inflation in our cost analyses.

Statistical Methods

The primary endpoint of this study was to compare medical costs among recipients of MA and NMA MRD and UCB transplantation. We also wanted to explore factors that were associated with increased costs of transplantation. To simplify comparison among different transplant categories, especially because of the variation in patient selection, risks for transplant-related complications and overall outcomes, costs are presented as cost per-day survived (in dollars).

Data are described as proportions or as median with range or interquartile range (lowest quartile-highest quartile). Comparison of patient, disease, and transplant characteristics was performed using chi-square, Fisher's exact, or Wilcoxon's rank sum test as appropriate. Cumulative incidence of engraftment, TRM, and GVHD was calculated by treating deaths from other causes as competing risks. The Kaplan-Meier method was used to plot curves for overall survival (OS). Multivariate Cox regression analysis was performed for OS after including the following variables: transplant type (main effect variable), age at HCT, sex, Karnofsky performance status at HCT, disease risk, previous HCT, cytomegalovirus (CMV)

status, HLA-match, acute GVHD (aGVHD) (grade iii-iv), graft failure, dialysis, mechanical ventilation, and hepatic veno-occlusive disease (VOD). Event times were measured from date of transplantation to date of death or last contact.

Analysis of variance (ANOVA) method was used to compare costs among different transplant types and was adjusted for the following variables: age at HCT, Karnofsky performance status at HCT, disease risk, previous HCT, CMV status, aGVHD (grade iii-iv), graft failure, dialysis, mechanical ventilation, hepatic VOD, duration of hospital stay (days of initial and any subsequent hospitalizations), and number of total medical encounters (days of hospitalization and outpatient clinic visits). HLA-match status correlated with transplant type and was not included as a separate variable. There were no significant interactions between transplant type and other predictor variables included in the ANOVA models.

All *P*-values reported are 2 sided. Analyses were performed using the SAS 9.1 software (Cary, NC).

RESULTS

Patient and Transplant Characteristics

Patient, disease, and transplant characteristics of our cohort are described in Table 1. As expected, recipients of NMA conditioning were older than those who received MA conditioning. The majority of patients who underwent UCB HCT (95%) received 2 cord blood units to optimize cell dose. MRD recipients were more likely to receive a 6/6 HLA matched graft (93% versus 9% for UCB). UCB recipients had slower neutrophil and platelet engraftment, had higher incidence of graft failure, and were more likely to have longer hospital stay compared to MRD recipients. The rates of major complications (dialysis, mechanical ventilation, or hepatic VOD) were similar among all types of allogeneic HCT.

Patient Survival and Outcomes

Probability of OS and cumulative incidences of TRM and aGVHD (grade iii-iv) in the first 100 days posttransplant were comparable among the 4 types of allogeneic HCT (Table 2). Transplant type was not predictive for OS on multivariate analysis (Table 3). Factors independently associated with increased risk of overall mortality included graft failure (relative risk [RR] 3.6, 95% confidence intervals [CI] 2.2-5.9), need for dialysis (RR 2.1, 95% CI 1.4-3.3), and need for mechanical ventilation (RR 4.4, 95% CI 3.1-6.2).

Costs of Transplantation

The median total cost of transplantation (excluding graft acquisition costs) within the first 100 days was $137,112 (interquartile range [IQR], 97,658-225,430) for MA and $84,824 (IQR, 52,247-151,906) for NMA allogeneic HCT, respectively ($P < .001$). The median total cost for UCB HCT was $137,564 (IQR, $81,486-$256,451) compared with $83,583 (IQR, $60,783-$123,581) for MRD HCT ($p < .001$). UCB HCT using either MA or NMA conditioning was associated with significantly higher costs than MRD HCT (Table 4). The median cost per day survived was $1,016 for MA and $612 for NMA MRD HCT and was $2082 for MA and $1156 for NMA UCB HCT ($P < .001$). For purposes of comparison, the median cost per day survived for matched unrelated donor HCT was $1586 for MA and $650 for NMA conditioning; however, these patients were excluded from further analyses because of small patient numbers.

The categories of cost for different transplant types are summarized in Figure 1. In general, the major contributors of cost for all transplant types were room and board and pharmacy services. MA and NMA UCB HCT recipients had longer hospitalizations, and as a result, had higher costs for room and board compared to recipients of MRD HCT. Pharmacy and laboratory services are more likely to be utilized during inpatient stay, and, hence, costs for these services were higher following UCB HCT. Because UCB transplant recipients also had a longer time to platelet engraftment, it was associated with higher blood component costs.

The contribution of various cost categories to total costs did not differ significantly among patients with low, intermediate, or high costs of care (Figure 2). However, the contribution of costs for blood components was relatively higher among patients whose care was the most expensive (total cost per day survived in the highest tertile, >$1805) compared with those with the least total costs (total cost per day survived in the lowest tertile, <$830).

Predictors of Cost

In multivariate analysis that adjusted for various factors that could influence costs (Table 5), MA UCB HCT was associated with higher costs than MA MRD HCT, but this difference was marginally significant (RR 1.3, 95% CI 1.1-1.5, $P = .05$). Interestingly, the costs of NMA MRD and NMA UCB HCT were similar to those of MA MRD HCT. More important predictors of costs were graft failure, need for dialysis, need for mechanical ventilation, and very long hospital stay. This is summarized in Table 6 and Figure 3, which highlights that patients with total costs in the highest tertile had a higher proportion of these risk factors compared to those with costs in the middle or lowest tertiles.

The median total cost per day survived for 23 patients with graft failure (MRD = 2, UCB = 21) was

Table 1. Patient, Disease, and Transplant Characteristics

Variable	MA MRD	MA UCB	NMA MRD	NMA UCB	*P*-value
N	67	63	54	110	
Median age, years	47	32	57	51	<.01
Range	19-55	18-45	24-70	18-69	
Age					
≤50 years	45 (67%)	63 (100%)	17 (32%)	51 (46%)	<.01
>50 years	22 (33%)	0	37 (68%)	59 (54%)	
Sex					
Male	42 (63%)	35 (56%)	31 (57%)	64 (58%)	.86
Female	25 (37%)	28 (44%)	23 (43%)	46 (42%)	
KPS score at transplant					
90-100	58 (87%)	51 (81%)	37 (69%)	88 (80%)	.04
≤80	4 (6%)	4 (6%)	11 (20%)	16 (14%)	
Missing	5 (7%)	8 (13%)	6 (11%)	6 (6%)	
Diagnosis					
Acute myelogenous leukemia	20 (30%)	28 (44%)	19 (35%)	33 (30%)	<.01
Acute lymphoblastic leukemia	9 (13%)	18 (29%)	2 (4%)	6 (5%)	
Non-Hodgkin lymphoma	13 (19%)	8 (13%)	14 (26%)	23 (21%)	
Hodgkin lymphoma	2 (3%)	0	2 (4%)	15 (14%)	
Multiple myeloma	1 (2%)	1 (2%)	3 (6%)	3 (3%)	
Myelodysplastic syndrome	9 (13%)	1 (2%)	5 (9%)	16 (14%)	
Other	13 (19%)	7 (11%)	9 (17%)	14 (13%)	
Disease risk					
Standard	37 (55%)	24 (38%)	15 (28%)	38 (35%)	.01
High	30 (45%)	39 (62%)	39 (72%)	72 (65%)	
Previous transplant	0	0	15 (28%)	27 (24%)	<.01
CMV serological status					
Positive (donor or recipient)	30 (45%)	14 (22%)	24 (44%)	11 (10%)	<.01
Negative	37 (55%)	49 (78%)	30 (56%)	99 (90%)	
Graft source					<.01
Peripheral blood	63 (94%)		51 (94%)		
Bone marrow	4 (6%)		3 (6%)		
UCB		63 (100%)		110 (100%)	
Single UCB		3		5	
Double UCB		60		105	
HLA match*					
6/6	64 (95%)	6 (10%)	49 (91%)	9 (8%)	<.01
5/6	3 (5%)	17 (27%)	5 (9%)	31 (28%)	
4/6	0	40 (64%)	0	70 (64%)	
Median time to ANC engraftment, days	17	23	7	13	<.01
Range	9-26	7-38	0-30	0-60	
Median time to platelet engraftment, days	25	56	15	47	<.01
Range	13-70	33-100	0-100	0-100	
Graft failure	2 (3%)	12 (19%)	0	9 (8%)	<.01
Second graft infusion	0	4		3	
Medical encounters in first 100 days					
Median hospital stay, days	39	48	23	38	<.01
Interquartile range	30-47	40-76	18-37	26-60	
Median clinic visits, days	30	19	28	28	<.01
Interquartile range	17-38	9-32	13-38	9-38	
Median total encounters, days	73	75	54	70	<.01
Interquartile range	53-83	59-93	42-67	57-91	
Major complications					
Dialysis	9 (13%)	10 (16%)	4 (7%)	10 (9%)	.39
Mechanical ventilation	20 (30%)	25 (40%)	13 (24%)	28 (26%)	.19
Hepatic veno-occlusive disease	5 (8%)	1 (2%)	0	3 (3%)	.09
Median follow-up, months	31	25	38	25	
Range	12-53	12-50	12-53	12-49	

MRD indicates matched related donor; UCB, umbilical cord blood; MA, myeloablative; NMA, nonmyeloablative; KPS, Karnofsky performance status; CMV, cytomegalovirus; HLA, human leukocyte antigen; ANC, absolute neutrophil count.
*Worst match for recipients of double UCB transplant.

$6976 (IQR, 5074-8698). In comparison, the median cost per day survived for patients who did not experience graft failure was $1105 (IQR, 679-2149) ($P <$ .001). UCB HCT was associated with higher total costs even after patients with graft failure were excluded; median cost per day survived for MA and NMA MRD HCT recipients was $1005 and $612, whereas that for UCB HCT recipients was $1703 and $1115, respectively ($P < .001$).

Patients who received dialysis had a median total cost per day survived of $4764 (IQR, 1194-6976) compared to $1102 (IQR, 678-2209) among those who

Table 2. Univariate Analysis for Posttransplant Outcomes

100 Days Posttransplant Outcomes	MA MRD	MA UCB	NMA MRD	NMA UCB	*P*-Value
Overall survival	81 (71%-91%)	70 (59%-81%)	78 (67%-89%)	78 (70%-86%)	.95
Treatment-related mortality	21 (11%-31%)	29 (17%-40%)	20 (10%-31%)	19 (12%-27%)	.55
Grade iii-iv acute GVHD*	15 (6%-24%)	24 (13%-34%)	22 (11%-33%)	17 (10%-24%)	.45

MRD indicates matched related donor; UCB, umbilical cord blood; MA, myeloablative; NMA, nonmyeloablative; GVHD, graft-versus-host disease.
*Cumulative incidence estimate.

did not receive dialysis ($P < .001$). Similarly, patients who received and did not receive mechanical ventilation had total cost per day survived of $5099 (IQR, 1287-7570) and $977 (IQR, 614-1508), respectively ($P < .001$).

DISCUSSION

In our contemporary cohort of adult HCT recipients, we observed the absolute costs of MA and NMA UCB transplantation to be higher than MA and NMA MRD transplantation. However, the costs of transplantation were primarily driven by severe posttransplant complications (graft failure, dialysis, and mechanical ventilation) and prolonged inpatient stay. UCB recipients have longer time to neutrophil and platelet engraftment than MRD recipients. Because 1 of the main endpoints for hospital discharge is engraftment, it is not surprising that UCB recipients had longer inpatient stay with its associated costs (room and board, pharmacy services, laboratory services, and blood components). Also, graft failure was more common following UCB HCT. Graft failure does increase the duration of hospitalization, and prolonged pancytopenia can increase the risk of infectious complications and transfusion requirements with a resultant increase in costs. The cost of a second graft infusion, especially UCB, also adds to this expense. Because the rates of severe complications (excluding graft failure) were similar among the 4 groups, the cost differences between MRD and UCB are more likely a result of prolonged hospitalization because of delayed engraftment and graft failure rather than complications. Our study did not address long-term costs of UCB transplantation. There is emerging data that UCB HCT is associated with a lower risk of chronic GVHD (cGVHD) [14,17]. Whether this would translate to lower or comparable costs versus MRD or matched unrelated donor HCT over an extended period of time needs to be investigated.

The use of less intense NMA conditioning does not necessarily translate to lower costs. In our study, the cumulative incidence of TRM was similar between all allogeneic transplant types, regardless of donor source or conditioning regimen intensity. Also, there was no difference in the rates of severe aGVHD, dialysis, mechanical ventilation, or hepatic VOD. Therefore, the older age and/or poor health status of NMA HCT recipients may offset the lesser toxicity of a reduced-intensity conditioning (RIC) regimen. We observed similar costs for MA and NMA MRD HCT. The occurrence of severe complications was a more important

Table 3. Multivariate Analysis for Overall Survival at 100 Days

Variables*	Relative Risk (95% Confidence Intervals)	*P*-Value
Transplant type		
MA MRD	1.0	.59
MA UCB	1.1 (0.7-1.6)	.85
NMA MRD	0.8 (0.5-1.2)	.21
NMA UCB	1.0 (0.6-1.5)	.98
Graft failure		
No	1.0	<.001
Yes	3.6 (2.2-5.9)	
Dialysis		
No	1.0	.001
Yes	2.1 (1.4-3.3)	
Mechanical ventilation		
No	1.0	<.001
Yes	4.4 (3.1-6.2)	

MRD, matched-related donor; UCB, umbilical cord blood; MA, myeloablative; NMA, nonmyeloablative.
*Other variables considered in the model included age at transplantation, sex, KPS score at transplantation, disease risk, history of previous transplant, CMV status, HLA match, graft source, acute graft-versus-host disease, and occurrence of hepatic veno-occlusive disease.

Table 4. Costs of Allogeneic Hematopoietic Cell Transplantation

		Cost per Day Survived, $	
Transplant Type*	N	Median	Interquartile Range
Myeloablative			
MRD	67	1016	796-2232
UCB	63	2082	1306-6219
MUD†	7	1586	1282-3892
Nonmyeloablative			
MRD	54	612	473-1023
UCB	110	1156	616-2472
MUD†	5	650	618-703

MRD indicates matched related donor; UCB, umbilical cord blood; MUD, matched unrelated donor.
*Excluding costs of graft acquisition.
†Recipients of matched unrelated donor grafts were excluded from further analyses.

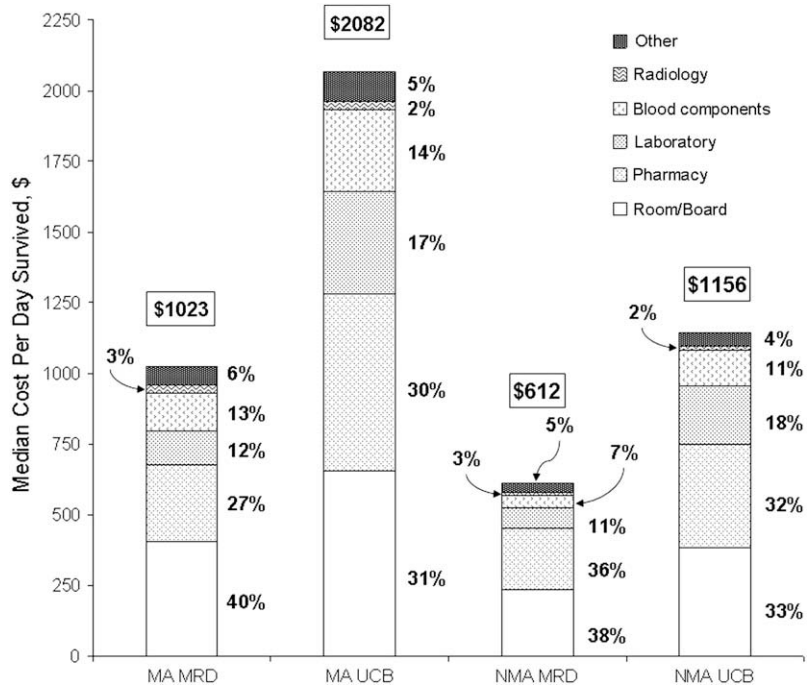

Figure 1. Costs of transplantation by transplant type. Column height represents median costs per day survived. Categories of costs (as percent) for each transplant type are also shown. Costs of graft acquisition were not included in this figure. (MA MRD, myeloablative matched related donor; MA UCB, myeloablative umbilical cord blood; NMA MRD, nonmyeloablative matched related donor and NMA UCB, nonmyeloablative umbilical cord blood transplantation).

driver of costs than conditioning regimen intensity. Other investigators have recently conducted cost analyses comparing MA and NMA HCT. Saito et al. [8] included 90 NMA and 185 MA HCT recipients transplanted between 2000 and 2003 in their retrospective analysis. They showed that NMA HCT costs approximately $53,030 less, and was associated with 16 fewer days of hospitalization than myeloablative HCT within the first year after transplantation. In another study, Cordonnier et al. [2] evaluated the 1-year costs of transplantation in 11 NMA and 12 MA HCT recipients with acute myelogenous leukemia (AML) who were enrolled on a prospective trial between 1998 and 2003. There was a trend toward lower costs of transplantation in the first 6 months for NMA conditioning, but the costs from 6-12 months were higher because of late complications and readmissions and there was no difference in the costs of NMA and

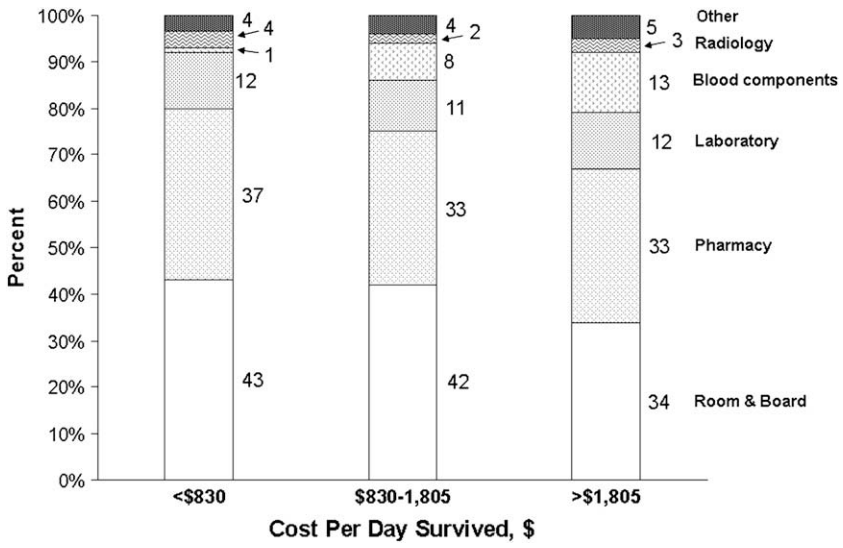

Figure 2. Categories of costs by tertiles of cost per day survived. The contribution of each category to total cost is represented as percent. Costs of graft acquisition were excluded from this figure.

Table 5. Multivariate Analysis for Predictors of Costs of Allogeneic Transplantation

Variables*†	Relative Risk (95% Confidence Intervals)	*P*-Value
Transplant type		
MA MRD	1.0	
MA UCB	1.3 (1.1-1.5)	.05
NMA MRD	1.0 (0.9-1.2)	.82
NMA UCB	1.0 (0.8-1.2)	.96
Graft failure		
No	1.0	
Yes	1.8 (1.7-1.9)	<.001
Dialysis		
No	1.0	
Yes	1.3 (1.1-1.5)	.05
Mechanical ventilation		
No	1.0	
Yes	1.3 (1.2-1.4)	.004
Hospital stay, tertiles‡		
<32 days	1.0	
32-48 days	1.0 (0.8-1.2)	.98
>48 days	2.1 (1.9-2.3)	<.001

MRD indicates matched related donor; UCB, umbilical cord blood; MA, myeloablative; NMA, nonmyeloablative.

*Other variables considered in the model included age at transplantation, KPS score at transplantation, disease risk, history of previous transplant, CMV status, acute graft-versus-host disease, hepatic veno-occlusive disease, and total medical encounters in days (by tertiles). Graft source and HLA match correlated with transplant type and were not included in the models as separate variables.

†Excluding costs of graft acquisition.

‡Total hospital stay in first 100 days posttransplantation.

Table 6. Key Patient and Transplant Characteristics Described by Cost Tertiles

Variable	Cost per day Survived (Tertiles)		
	<$830	$803-1805	>$1805
N	98	98	98
Median age in years (range)	51 (22-69)	44 (18-69)	44 (18-68)
KPS score at transplant ≤80	10	7	18
High disease risk	68	59	53
Previous transplant	12	12	18
CMV positive (donor or recipient)	31	27	21
Conditioning regimen and donor source			
MA MRD	23	28	16
NMA MRD	35	12	7
MA UCB	2	25	36
NMA UCB	38	33	39
Median time to ANC engraftment in days (range)	8 (0-38)	17 (0-32)	17 (5-60)
Graft failure	1	1	21
Major complications			
Dialysis	4	8	21
Mechanical ventilation	10	16	60
Hepatic veno-occlusive disease	1	2	6
Grade iii-iv acute GVHD	17	15	15
Median duration of hospital stay (interquartile range)	23 (17-35)	40 (35-47)	61 (40-82)

KPS indicates Karnofsky performance status; CMV, cytomegalovirus; MRD, matched related donor; UCB, umbilical cord blood; MA, myeloablative; NMA, nonmyeloablative; ANC, absolute neutrophil count; GVHD, graft-versus-host disease.

MA HCT at 1 year posttransplantation. Differences in patient population and transplant techniques (eg, conditioning regimens) could explain the discrepant results from our and these 2 published studies. Some observational studies have shown equivalent long-term survival among patients receiving MA and NMA HCT for selected diseases [16,18,19]. With similar outcomes, the transplant modality with lesser costs and lesser morbidity would be preferred. Hence, more studies to better understand cost differences between MA and NMA conditioning regimens are needed and any randomized trials comparing these 2 modalities should include economic and quality of life endpoints.

The role of complications in increasing costs of transplantation has been described previously. In a study of 315 MA allogeneic HCT recipients transplanted between 2000 and 2004, [7]. showed that the mean cost of transplantation in their cohort was $79,222, but severe complications increased total costs by an average of $20,228. [5]. have also shown that complications are associated with higher costs. Their study included 181 patients who received a n MA allogeneic HCT between 1994 and 1997; the median initial inpatient cost was $105,300 and occurrence of infection, hepatic VOD, aGVHD, and death were predicted to add between $15,300 and $28,100 each to the costs of transplantation. Prevention and early recognition and management of complications, where possible, can decrease the costs of transplantation. Esperou et al. [3], in a study of 85 MA allogeneic HCT recipients from 1998-2000, have also shown that predictors of higher costs (adding an average €20,000/patient) include transplant related complications, GVHD, and repeated infections.

Several limitations have to be considered in the interpretation of our analysis. There exists considerable practice variation in HCT among transplant centers, and our results may not be generalizable. Also, we captured costs within the first 100 days following transplantation and did not consider costs of long-term care or management of cGVHD and its complications. Other studies have shown that the costs of transplantation are largely concentrated within the first 100 days [7]. We selected the early posttransplant period for investigation because all medical care is conducted exclusively at our center. Nevertheless, we could not account for costs of outpatient prescription drugs and home-care services. Transplant conditioning and GVHD prophylaxis and management regimens were dictated by specific protocols, and supportive care was based on established guidelines, limiting the impact of practice variation on costs.

We excluded costs of graft acquisition in cost analyses because the characteristics of graft procurement, storage, and processing are very different for MRD and UCB. Given the resources needed for UCB collection and storage, UCB graft acquisition is much more expensive than MRD. The contribution of graft

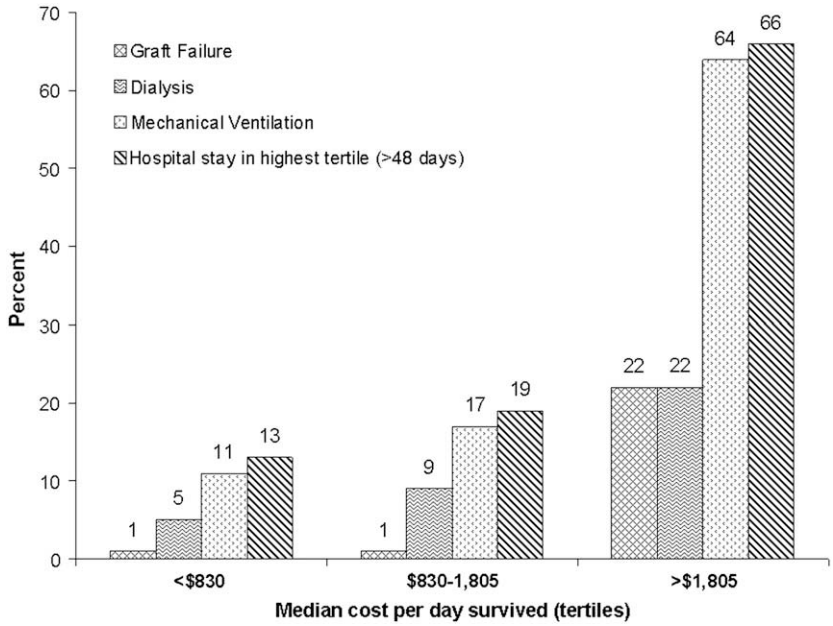

Figure 3. Predictors of costs of transplantation. Graft failure, dialysis use, use of mechanical ventilation, and prolonged hospital stay were associated with increased costs. Costs of graft acquisition were not included in this figure. Column height represents proportion of patients within each group.

acquisition costs to total costs cannot be ignored, especially because of its large dollar amount, and any strategies to increase the cost effectiveness of UCB HCT will also have to address these costs.

Because of the relatively small number of patients who received a matched unrelated donor HCT, we could not perform detailed analyses comparing costs between matched unrelated donor and UCB transplantation. Because UCB is primarily considered among various alternative donor options for patients without an MRD, future cost analyses comparing matched unrelated donor and UCB HCT will be important. In our unadjusted descriptive analysis, transplantation with matched unrelated donor was more expensive than MRD but less expensive then UCB for both MA and NMA conditioning regimens.

In conclusion, allogeneic HCT is a costly procedure. In the first 100 days after transplantation, the costs of MA and NMA MRD and nonmyeloablative UCB transplantation are similar, whereas MA UCB HCT is more expensive. Severe complications, graft failure, and prolonged hospitalization are the major contributors to total costs in the early posttransplant period. Increased costs of UCB HCT are primarily because of longer hospitalization for delayed engraftment and graft failure. Strategies to decrease the risk of severe complications would reduce the overall costs of transplantation in general. Methods to enhance engraftment and decrease the risk of graft failure in recipients of UCB HCT would make this procedure more cost effective.

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